REMARKS

Claims 94 and 108-109, and 117-120 are currently pending in the application. No new matter has been introduced by virtue of the within response.

The Advisory Action dated December 2, 2004 (the "Advisory Action") confirmed entry of the amendments proposed in the Amendment After Final Rejection filed on November 9, 2004 (the "First Amendment After Final Rejection").

The Advisory Action also indicated that the §102(b) rejection had been overcome by the First Amendment After Final Rejection. However, the §103(a) rejections – over Sakanaka, Masahiro, Zhang and Tamiko - were maintained. In particular, the position was taken that the amounts recited in the claims of the present application would have been obvious in view of the cited art. The Advisory Action notes that the claimed dosages are less than the dosages described in the cited art. Thus, the position is taken that the dosages recited in the claims of the present application are intrinsic to the doses disclosed in the prior art and therefore would allegedly intrinsically perform the intended method of use.

The Advisory Action Before Filing of an Appeal Brief dated April 29, 2005 (The "Second Advisory Action") refused entry of the Amendment and Rule 1.132 Declaration filed February 28, 2005. In particular, the position was taken that the data of the Declaration and the Zhang document were contradictory such that the declaration did not support a holding of unexpected results.

Thus, Examiner averred in the Second Advisory Action that "Zhang, et al. clearly taught that the same procedure resulted in a 22% decrease in occlusion for 10 mg Rb_1/kg/day and a 50% decrease in occlusion for 40 Rb_1 mg/kg/day (see Table 1, p. 46)." The Examiner concludes that there has been an error in the protocol of the experiment of the Declaration because there is a contradiction with the experimental result shown in Zhang et al. However, Applicants

respectfully submit that the conclusions reached by the Examiner are not proper due to improper comparisons between the data presented in Zhang and in the Declaration. That is, the Zhang data were obtained by different disease modes, different administration methods and different indications. More particularly, a list of the differences between Zhang and the Declaration, include:

1. The Examiner relies upon a 2-h MCAO experiment with administration of Rb_1 *prior* to ischemia in the Zhang document in order to assert that higher doses of Rb_1 offer increased efficacy.
2. Zhang teaches a permanent MCAO experiment with administration of 10, 20, or 40 mg/kg of Rb_1 *prior* to ischemia. The administration of Rb_1 at the indicated doses did not provide a statistically significant decrease in infarct size when compared to the control.
3. In contrast, the Declaration recites data for a permanent MCAO experiment in which Rb_1 administration occurred two (2) hours post ischemia.
4. The experiments of the Declaration show that for permanent MCAO ischemia, lower does of Rb_1, e.g., 6μg/day or 60 μg/day provide superior reduction in infarct size (measured by volume) compared to higher does of Rb_1, e.g., 3 mg/day or 12 mg/day. See Figure 3 of the Declaration, which figure has a header in the Japanese language.

Therefore the Examiner's comparison of Zhang and the Declaration is not correct.

As the document is understood, Zhang teaches that in permanent MCAO, 40 Rb_1 mg/kg/day reduced IS (Infarct size) by 14% with ivB (IV before MCAO) (see, page 46, line 17-18 of the left column and Table 1; a marked up copy of 46 of Zhang is attached). Zhang also teaches that in the case of 2h-MCAO, Rb_1 20 to 40 mg/kg intravenous before ischemia was more effective than after ischemia (see, page 46, line 22-23 of the left column and Table 1; a marked up copy of 46 of Zhang is attached).

In contrast, the Declaration provides that the intravenous administration of 40 Rb_1 mg/kg/day two (2) hours after MCAO reduced infarct size (IS) by about 9% (Calculated from table 3). The Declaration recites a 9% reduction in infarct size when Rb_1 is administered post-ischemia, which is consistent with Zhang's report of a 14% reduction when Rb_1 is administered prior to ischemia. Thus, the Declaration does not contradict the data of Zhang.

As discussed *supra*, there is no contradiction between the results of the Declaration and the Zhang document, there is no error in the protocol of the experiments recited in the Declaration. Therefore, the Declaration provides evidence that the lower dose of Rb_1 provides an unexpected therapeutic result based on the prior art teachings.

The rejections are traversed. Even if combined, the cited references fail to teach or suggest the methods of the present invention in a manner sufficient to maintain the §103(a) rejection.

The arguments and remarks originally presented in the second amendment after final action filed February 28, 2005 are represented *infra* to insure their entry and consideration in the instant application.

Referring first to Sakanaka and Masahiro, these references recite that crude saponin fraction(s) of ginseng and ginsenoside Rbl when administered by the dosage and administration routine disclosed therein have the effect of preventing brain ischemia.

Sakanaka and Masahiro teach that **elevated doses** of crude saponin fraction(s) of ginseng and ginsenoside Rbl recited by Masahiro and Sakanaka may be effective to cerebrovascular disorder or cerebral infarction by these **elevated dosages**. Moreover, each of Masahiro and Sakanaka teach that with regard to the dosage for the preventive effect of crude saponin fraction(s) of ginseng, 100mg/kg/day is superior to 50mg/kg/day, and with regard to ginsenoside Rbl, 20mg/kg/day is superior to 10mg/kg/day. In short, these references teach that elevated

dosages are superior. In that way, the references effectively teach away from the present invention.

Clearly, one skilled in the art would not have been motivated to decrease the dosages below the ranges recited in Sakanaka and Masahiro. The Final Office Action cites MPEP§2144.05 Part II A for the premise that modification of dosage amount is routine experimentation. However, the instant claims provide methods of treatment of or prevention of diseases causing apoptosis or apoptosis-like death of cells by administration of a doses or dosages of ginseng extracts are adjusted to between 145 pg/kg/day and 1450 μg/kg/day, and those of ginseng components are adjusted to between 1.67 pg/kg/day and 1.67 mg/kg/day. The dose or dosage provided by claim 94 (as amended by the First Amendment After Final Rejection), is at least one order of magnitude lower than those recited in Sakanaka or Masahiro. Moreover, Sakanaka and Masahiro teach that higher dosages provide greater therapeutic effect. Thus, although some modification of dosage may be reasonable, at the time the invention was made, one of ordinary skill in the art would have been directed by the teaching and suggestion of Sakanaka or Masahiro to increase, not decrease, the dosage of red ginseng to a patient susceptible to ischemia.

In contrast, Applicants have surprisingly discovered that mammals suffering from spinal cord injury or cerebral infarction can be treated by administration of crude saponin fraction(s) of ginseng and/or ginsenoside Rbl (which is one of the ginsenoside compositions) at unprecedented low dosage.

Additionally, in support of the arguments stated herein, attention is directed to the enclosed **Rule 132 Declaration of Masahiro Sakanaka**. The Rule 132 Declaration details certain experiments conducted to compare the therapeutic effect of ginsenoside Rb1 administered in low-dosage form according to the present invention with that of ginsenoside Rb1 administered in high dosage form, e.g., as in the cited art. The evidence provided in the Rule 132 Declaration

shows the that the low-dosage ginsenoside Rb1 is highly superior to the high-dosage ginsenoside Rb1 in terms of the clinically applicable therapeutic time window. Such an effect is very surprising and non-obvious in view of the art cited. The evidence provided rebuts any case of alleged obviousness that may be contended.

As discussed *supra*, the Declaration does not contradict the data of Zhang. Thus, the Declaration provides evidence of unexpected results for the claimed invention.

It is respectfully submitted, therefore, that claim 94 is patentable and non-obvious over Sakanaka, Masahiro, or any combination thereof. Claims 108, 109, and 117-120 depend from claim 94 and are therefore also patentable over Sakanaka, Masahiro, or any combination thereof.

Turning now to the Zhang reference, that disclosure merely teaches the amelioration to cerebral infarction by intravenous administration of ginsenoside Rbl at a dose of 10mg/kg/day or 40mg/kg/day. However Zhang recites that ginsenoside Rbl administered at 10mg/kg/day provides only a preventive benefit and that administration at 40 mg/kg/day provides preventive and slight therapeutic benefit. Thus, Zhang teaches that increased dosages of ginsenoside Rbl are preferred for treatment and prevention of cerebral infarction such that one skilled in the art would not have been motivated to increase therapeutic or preventative effect by reducing the administered dosage.

In contrast, Applicants have surprisingly discovered a decent effect on cerebral infarction rat by intravenous administration of an unprecedentedly low dose of 20 μg/kg/day or 200 μg/kg/day. Thus, Applicants have discovered that at dosages of 20 μg/kg/day or 200 μg/kg/day decrease the lesion size of cerebral infarction by one third to one fourth relative to a control lesion. Furthermore, said therapeutic effect is obviously superior to the effect shown by Zhang et al.

One skilled in the art would not have found motivation from the Zhang disclosure to

reduce the dosage of ginsenoside Rb1 to a patient to provide superior therapeutic effect at least because Zhang teaches that higher doses of ginsenoside Rb1 offer superior therapeutic effect against cerebral infarction.

Again, reference is directed to the enclosed **Rule 132 Declaration** to further rebut any case of obviousness that may be contended in view of Zhang.

As discussed *supra*, the Declaration does not contradict the data of Zhang. Thus, the Declaration provides evidence of unexpected results for the claimed invention.

Therefore claim 94, as amended, is patentable and non-obvious over Zhang. Claims 108, 109, and 117-120 depend from claim 94 and are therefore also patentable over Zhang.

Claims 94, 108-109, and 115-120 stand rejected under 35 U.S.C. §103(a) over Tamiko.

Claim 94, as amended, is patentable over Tamiko. Claims 108, 109, and 117-120 depend from claim 94 and are therefore also patentable over Tamiko.

The claims of the present application provide methods of treating a mammal suffering from or susceptible to diseases causing apoptosis or apoptosis-like death of cells, except for treatment of immune deficiency, which comprises administering to the mammal a composition comprising ginseng extracts, or ginseng components, its metabolites or salts thereof. Thus, the claims do not provide methods of treatment comprising administration of ginseng. Therefore claims 94, 108, 109, 117-120 are patentable over Tamiko.

The rejections are therefore properly withdrawn. For instance, it is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references to make the claimed invention, nor is there a reasonable expectation of success.

In view thereof, reconsideration and withdrawal of the §103 rejections are requested.

Allowance of claims 94 and 108-120 is respectfully requested in view of the foregoing discussion and the enclosed Rule 132 Declaration. This case is believed to be in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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